Essential Psychopharmacology
Neuroscientific Basis and Practical Applications
Second Edition
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CHAPTER 7

NEWER ANTIDEPRESSANTS AND MOOD STABILIZERS

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In this chapter, we will continue our review of pharmacological concepts underlying the use of antidepressant and mood-stabilizing drugs. The goal of this chapter is to acquaint the reader with current ideas about how several of the newer antidepressants work. We will also introduce ideas about the pharmacologic mechanism of action of the mood stabilizers. As in Chapter 6, we will explain the mechanisms of action of these drugs by building on general pharmacological concepts.

Our treatment of antidepressants in this chapter continues at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice.

Discussion of antidepressants and mood stabilizers will begin with the antidepressants that act by a dual pharmacological mechanism, including dual reuptake blockade, alpha 2 antagonism and dual serotonin 2A antagonism/serotonin reuptake blockade. We will also explore several antidepressants under development but not
yet introduced into clinical practice. Next, we will introduce the use of lithium and anticonvulsants as mood stabilizers. Finally, we will discuss the use of combinations of drugs and briefly mention electroconvulsive therapy (ECT) and psychotherapy for the treatment of mood disorders.

**Dual Serotonin and Norepinephrine Reuptake Inhibitors**

One class of antidepressants that combines the actions of both the selective serotonin reuptake inhibitors (SSRIs) and the selective noreadrenergic reuptake inhibitors (NRIs) is the class of dual serotonin and noreadrenergic reuptake inhibitors (SNRIs) (Fig. 7 — 1). The designation "dual reuptake inhibitors" can be confusing because many tricyclic antidepressants (TCAs) are also dual reuptake inhibitors of both norepinephrine (NE) and serotonin (5-hydroxytryptamine [5HT]). What is unique about venlafaxine, the prototypical SNRI, is that it shares the NE and 5HT, and to a lesser extent dopamine (DA) reuptake inhibitory properties of the classical TCAs (Fig. 7 — 1), but without alpha 1, cholinergic, or histamine receptor blocking properties (see Figs. 6—30 to 6—32). Thus, SNRIs are not only dual-action agents, but they are **selective** for this dual action. Dual-action SNRIs thus have the properties of an SSRI and a selective NRI added together in the same molecule.

Venlafaxine is the only dual-action SNRI currently marketed. Depending on the dose, it has different degrees of inhibition of 5HT reuptake (most potent and there-
fore present at low doses), NE reuptake (moderate potency and therefore present at higher doses) and DA reuptake (least potent and therefore present only at highest doses) (Fig. 7—2). However, there are no significant actions on other receptors. Venlafaxine is now available in an extended-release formulation (venlafaxine XR), which not only allows once daily administration but also significantly reduces side effects, especially nausea. The increased tolerability of venlafaxine in this new formulation is important, especially considering the trend in psychiatry to use higher doses of venlafaxine XR to exploit both the NE and the 5HT mechanism.

Additional dual 5HT-NE reuptake inhibitors include sibutramine, which is approved for the treatment of obesity but not depression. Tramadol is a kappa opiate agonist approved for the treatment of pain, but it also has serotonin and norepinephrine reuptake inhibitor properties. Dual reuptake inhibitors in clinical testing as antidepressants include milnacipran and duloxetine.

Are two antidepressant mechanisms better than one? The original tricyclic antidepressants have multiple pharmacological mechanisms and are termed "dirty drugs" because many of these mechanisms were undesirable, as they cause side effects (Fig. —3). The idea was then to "clean up" these agents by making them selective, and thus the SSRI era was born. Indeed, developing such selective agents made them devoid of pharmacologic properties that mediated anticholinergic, antihistaminic, and antiadrenergic side effects (Fig. 7 — 3). However, selectivity may sometimes be less desired than multiple pharmacologic mechanisms, as in difficult cases that are

**SNRI ACTIONS**

![SNRI ACTIONS](image)

**FIGURE 7 — 2.** In this diagram, the dual actions of the serotonin/norepinephrine reuptake inhibitors (**SNRIs**) are shown. Both the norepinephrine reuptake inhibitor (**NRI**) portion of the SNRI molecule (left panel) and the serotonin reuptake inhibitor (**SRI**) portion of the SNRI molecule are inserted into their respective reuptake pumps. Consequently, both reuptake pumps are blocked, and the drug mediates an **antidepressant effect.** This is analogous to two of the dimensions of the tricyclic antidepressants (**TCAs**), already shown in Figures 6 — 28 and 6 — 29. It is also analogous to the single action of SSRIs (Fig. 6 — 33) added to the single action of the selective NRIs (Figure 6—46).
Are two mechanisms better than one for some antidepressants? Originally, multiple mechanisms were synonymous with "dirty drugs" because they implied unwanted side effects. This is shown as tricyclic antidepressants on the left. The trend to develop selective drugs (center) led to removal of unwanted side effects. More recently, the trend has again been to add multiple mechanisms together to improve tolerability and enhance efficacy. Enhanced efficacy from synergistic pharmacological mechanisms can apparently increase therapeutic responses in some patients, especially those resistant to single-mechanism agents.

Thus, not only are dual-reuptake inhibitors effective antidepressants, but they may have some therapeutic advantages over the SSRIs. Theoretically, the addition of NE, and to a lesser extent DA, reuptake blockade to 5HT reuptake blockade (Fig. 7—2) might lead to pharmacological synergy among these neurotransmitter systems and thus boost efficacy. Synergy is the working together of two or more mechanisms so that the total efficacy is greater than the sum of its parts (in other words, $1 + 1 = 10$).

The molecular basis of this synergy may be manifest at the level of genetic expression. Thus, beta-adrenergic receptor stimulation by NE results in gene expression, as discussed previously and shown in Figure 7—4. However, in the presence of
FIGURE 7—4. Shown here are the theoretical **therapeutic actions** of selective serotonin antidepressants on **gene expression**. The purple norepinephrine (NE) at the top (top red circle) is causing a cascade of biochemical events resulting in the transcription of a neuron's genes (mRNAs in the bottom circle). The noradrenergic receptor is linked to a stimulatory G protein (Gs), which is linked in turn to the enzyme adenylate cyclase (AC), which converts ATP into the second messenger cAMP. Next, cAMP activates protein kinase A (PKA), which then activates a transcription factor such as cyclic AMP response element binding (CREB) protein.

Simultaneous serotonin 2A receptor stimulation by serotonin, gene expression is amplified synergistically (Fig. 7—5). Thus, norepinephrine and serotonin may work together to produce critical expression of genes in a manner that does not occur when either works alone. This could theoretically explain why dual 5HT-NE reuptake blockade may produce synergistic antidepressant effects in some patients.

Indications that there may be antidepressant synergy from dual 5HT-NE actions that correspond with these theoretical molecular events come from studies in which venlafaxine has produced increased remission rates in major depressive disorders as compared with SSRIs. Increased remission rates with the TCAs over the SSRIs have also been reported and support the concept of dual action being more efficacious than SSRI action alone for remission of depression in some patients.

Another indication that the dual mechanisms may lead to more efficacy is the finding that venlafaxine seems to have greater efficacy as the dose increases, whereas other antidepressants seem to have little difference in efficacy at higher doses. Since the noradrenergic (and dopaminergic) action of venlafaxine is greater at higher doses, this suggests that there is more and more efficacy as the second mechanism becomes active (i.e., the noradrenergic "boost"). This also supports the rationale for using dual mechanisms for the most difficult patients, (i.e., those who are treatment-resistant to SSRIs and other antidepressants and those who are responders but not remitters to SSRIs or other antidepressants).
FIGURE 7 — 5. When serotonin (5HT) and norepinephrine (NE) act synergistically to enhance gene expression (compare with Fig. 7-4), this theoretically results in enhanced therapeutic efficacy in depression. Thus, the cascade on the left (shown also in Fig. 7-4) here is occurring simultaneously with the activation of the cascade on the right. Serotonin (top red circle) is thus working with NE on the left to cause even more gene activation (mRNAs in the bottom red circle) than NE can cause by itself in Figure 7-4. This is synergy. The 5HT receptor here is coupled to a stimulatory G protein (Gs), which activates the enzyme phospholipase C (PLC) to convert phosphatidyl inositol (PI) to diacylglycerol (DAG) and activate calcium flux, so that protein kinase C (PKC) can increase the transcription of neuronal genes by working synergistically at the level of transcription factors (TF).

Other information suggesting therapeutic advantages for dual mechanisms is the finding that the SNRI venlafaxine XR is an effective generalized anxiolytic. That is, among the known antidepressants only venlafaxine XR is approved as a generalized anxiolytic as well as an antidepressant. Such actions might have the favorable therapeutic consequences of converting anxious depression into complete remission of both depression and anxiety. Additional support for the role of dual SNRI action yielding enhanced efficacy in both depression and anxiety comes from evidence that the dual-action but nonselective tricyclic antidepressants also appear to be effective as generalized anxiolytics but have never been marketed for this indication. Dual-action mirtazapine may also have some generalized anxiolytic effects (see below).

There are a number of ways to implement this dual mechanism strategy beyond just using higher doses of venlafaxine XR. One of these is to use other dual 5HT7 NE—acting antidepressants, such as mirtazapine, discussed below, or possibly even going back to certain tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs). Another would be to use pharmacologically rational combinations of drugs with potentially synergistic mechanisms. An obvious example of how to deliver dual serotonin and noradrenergic reuptake inhibition would be to add reboxetine to an SSRI. This and other dual mechanism strategies will be discussed in further detail in the section on antidepressant combinations.
FIGURE 7 — 6. **Alpha 2 antagonists** (red circle) can increase noradrenergic neurotransmission by "cutting the brake cable" for noradrenergic neurons. That is, alpha 2 antagonists block presynaptic alpha 2 autoreceptors (red circle), which are the "brakes" on noradrenergic neurons. This causes noradrenergic neurons to become disinhibited, since norepinephrine (NE) can no longer block its own release. Thus, **noradrenergic neurotransmission is enhanced**.

**Dual Serotonin and Norepinephrine Actions Via Alpha 2 Antagonism**

Blocking the reuptake pump for monoamines or the enzyme monoamine oxidase (MAO) are not the only mechanisms to increase serotonin and norepinephrine. Another way to raise both serotonin and norepinephrine levels is to block alpha 2 receptors. Recall that norepinephrine turns off its own release by interacting with presynaptic alpha 2 autoreceptors on noreadrenergic neurons (Fig. 5 — 21); norepinephrine also turns off serotonin release by interacting with presynaptic alpha 2 heteroreceptors on serotonergic neurons (Fig. 5—44). If an alpha 2 antagonist is administered, norepinephrine can no longer turn off its own release, and noradrenergic neurons are thus disinhibited (Fig. 7 — 6). That is, the alpha 2 antagonist "cuts the brake cable" of the noradrenergic neuron, and norepinephrine release is thereby increased.

Similarly, alpha 2 antagonists do not allow norepinephrine to turn off serotonin release. Therefore, serotonergic neurons become disinhibited (Fig. 7—7). Similarly to their actions at noradrenergic neurons, alpha 2 antagonists act at serotonergic neurons to "cut the brake cable" of noradrenergic inhibition norepinephrine brake on serotonin shown in Figs. 5—47 and 5—48. Serotonin release is therefore increased (Fig. 7-7).

A second mechanism to increase serotonin release after administration of an alpha 2 antagonist may be even more important. Recall that norepinephrine neurons from the locus coeruleus innervate the cell bodies of serotonergic neurons in the midbrain raphe (Figs. 5—47 and 5-48). This noradrenergic input enhances serotonin release.
Alpha 2 antagonists can also increase serotonergic neurotransmission by "cutting the brake cable" for serotonergic neurons (compare with Fig. 7 — 6). That is, alpha 2 antagonists block presynaptic alpha 2 heteroreceptors (red circle), the "brakes" on serotonergic neurons. This causes serotonergic neurons to become disinhibited, since norepinephrine (NE) can no longer block serotonin (5HT) release. Thus, serotonergic neurotransmission is enhanced.

via a postsynaptic alpha 1 receptor. Thus, when norepinephrine is disinhibited in the noradrenergic pathway to the raphe, the norepinephrine release there will increase and cause alpha 1 receptors to be stimulated, thereby provoking more serotonin release (Fig. 7—8). This is like stepping on the serotonin accelerator. Thus, alpha 2 antagonists both cut the brake cable and step on the accelerator for serotonin release (Fig. 7-9).

Alpha 2 antagonist actions thus yield dual enhancement of both serotonin and norepinephrine release (Fig. 7 — 10). Although no selective alpha 2 antagonist is available for use as an antidepressant, one drug with prominent alpha 2 properties, namely mirtazapine, is available worldwide as an antidepressant (Fig. 7 — 10). Mirtazapine does not block any monoamine transporter, but in addition to its potent antagonist actions on alpha 2 receptors it also has antagonist actions at serotonin 2A, 2C, and 3 receptors and histamine 1 receptors (Fig. 7 — 10). The 5HT2A antagonist properties may contribute to mirtazapine's antidepressant actions (Fig. 7 — 11). and these serotonin 2A antagonist properties as well as serotonin 2C antagonist and H1 antihistamine properties may contribute to its anxiolytic and sedative hypnentic properties (Figs. 7 — 11 to 7 — 13). By blocking serotonin 2A, 2C, and 3 receptors, the side effects associated with stimulating them, especially anxiety, nausea, and sexual dysfunction are avoided (Fig. 7 — 11). However, blocking serotonin 2A and H1 antihistamine receptors accounts for the side effect of sedation, and blocking serotonin 2C and H1 receptors accounts for the side effect of weight gain (Fig. 7-12).
FIGURE 7 — 8. **Alpha 2 antagonists** can also increase serotonergic neurotransmission by “stepping on the serotonin (5HT) accelerator.” That is, norepinephrine (NE) input for the locus coeruleus (bottom) to the cell bodies of serotonergic neurons in the midbrain raphe synapse on postsynaptic excitatory alpha 1 receptors. This increases serotonergic neuronal firing and serotonin release from the serotonin nerve terminal on the right.

The therapeutic actions of mirtazapine are thought to be mainly mediated through its alpha 2 antagonist properties. As mentioned above, by blocking presynaptic alpha 2 receptors, mirtazapine cuts the brake cable and disinhibits both serotonin and norepinephrine release; by disinhibiting norepinephrine release, alpha 1 receptors are stimulated by norepinephrine, and serotonin release is enhanced by stepping on the serotonin accelerator (Fig. 7 — 13). An integrated view of all of mirtazapine’s pharmacologic actions is shown in Figure 7 — 13.

In addition to its efficacy as a first-line antidepressant, mirtazapine may have enhanced efficacy due to its dual mechanism of action (Fig. 7 — 3), especially in combination with other antidepressants that block serotonin and/or norepinephrine reuptake. This will be discussed below in the section on antidepressant combinations. Mirtazapine may also have utility in panic disorder, generalized anxiety disorder, and other anxiety disorders, but has not been intensively studied for these indications.

Two other alpha 2 antagonists are marketed as antidepressants in some countries (but not the United States), namely, mianserin (worldwide except in the United
This diagram shows how both **noradrenergic and serotonergic neurotransmission are enhanced by alpha 2 antagonists**. The noradrenergic neuron at the bottom is interacting with the serotonergic neuron at the top. The noradrenergic neuron is disinhibited at all of its axon terminals because an alpha 2 antagonist is blocking all of its presynaptic alpha 2 autoreceptors. Thus, this has the effect of "cutting the brake cables" for norepinephrine (NE) release at all of its noradrenergic nerve terminals (NE released in all three red circles). Serotonin (5HT) release is enhanced by NE via two distinct mechanisms. First, alpha 2 antagonists "step on the 5HT accelerator" when NE stimulates alpha 1 receptors on the 5HT cell body and dendrites (left red circle). Second, alpha 2 antagonists "cut the 5HT brake cable" when alpha 2 presynaptic heteroreceptors are blocked on the 5HT axon terminal (middle red circle).

Mianserin has alpha 1 antagonist properties, which mitigate the effects of enhancing serotonergic neurotransmission, so that this drug enhances predominantly noradrenergic neurotransmission, yet with associated 5HT2A, 5HT2C, 5HT3, and H1 antagonist properties. Yohimbine is also an alpha 2 antagonist, but its alpha 1 antagonist properties similarly mitigate its pro-monoaminergic actions. Several selective alpha 2 antagonists, including idazoxan and fluparoxan, have been tested, but they have not yet demonstrated robust antide-
FIGURE 7 — 10. Icon for mirtazapine, sometimes also called a noradrenergic and specific serotonergic antidepressant (NaSSA). Its primary therapeutic action is alpha 2 antagonism as shown in Figures 7-6 through 7-9. It also blocks three serotonin receptors: 5HT2A, 5HT2C, and 5HT3. Finally, it blocks H1 histamine receptors.

FIGURE 7 — 11. Mirtazapine actions at serotonin (5HT) synapses. When presynaptic alpha 2 heteroreceptors are blocked, 5HT is released, but it is directed to the 5HT1A receptor because 5HT actions at 5HT2A, 5HT2C, and 5HT3 receptors are blocked. The result is that antidepressant and anxiolytic actions are preserved but the side effects associated with stimulating 5HT2A, 5HT2C, and 5HT3 receptors are blocked. However, sedation and weight gain may result from these actions.
When mirtazapine blocks histamine 1 receptors, it can cause anxiolytic actions, but also sedation and weight gain as side effects.

Pressant efficacy and also are not always well tolerated because they can provoke panic, anxiety, and prolonged erections in men.

**Dual Serotonin 2 Antagonists/Serotonin Reuptake Inhibitors**

Several antidepressants share the ability to block serotonin 2A receptors as well as serotonin reuptake. In fact, some of the tricyclic antidepressants, such as amitriptyline, nortriptyline, doxepine, and especially amoxapine, have this combination of actions at the serotonin synapse. Since the potency of blockade of serotonin 2A receptors varies considerably among the tricyclics, it is not clear how important this action is to the therapeutic actions of tricyclic antidepressants in general.

However, there is another chemical class of antidepressants known as phenylpiperazines, which are more selective than the tricyclic antidepressants and whose most powerful pharmacological action is to block serotonin 2A receptors (Fig. 7 — 14). This includes the agents nefazodone and trazodone. Both of these agents also block serotonin reuptake but do so in a less potent manner than either the tricyclic antidepressants or the SSRIs (Fig. 7 — 15). Since the pharmacological mechanism of action of dual serotonin 2A antagonistserotonin reuptake inhibitors derives from a combination of powerful antagonism of serotonin 2A receptors with less powerful blockade of serotonin reuptake, these agents are classified separately as serotonin 2A antagonists/reuptake inhibitors (SARIs) (Figs. 7 — 14 and 7 — 15).

Nefazodone is the prototypical member of the SARI class of antidepressants. It is a powerful serotonin 2A antagonist with secondary actions as a serotonin and norepinephrine reuptake inhibitor (Figs. 7 — 14 and 7 — 15). Nefazodone also blocks alpha 1 receptors, but the clinical consequences of this are generally not important, perhaps because its norepinephrine reuptake inhibition reduces this action in vivo.

The major distinction between the SARIs and other classes of antidepressants is that SARIs are predominantly 5HT2A antagonists. A lesser but important amount
FIGURE 7-13. An *overview* of the actions of mirtazapine. This includes the actions of alpha 2 antagonists already shown in Figure 7—9, that is, the therapeutic actions of cutting the NE brake cable while stepping on the 5HT accelerator (left circle), as well as cutting the 5HT brake cable (middle circle). This increases both 5HT and NE neurotransmission. On the right are the additional actions of mirtazapine beyond alpha 2 antagonism. These postsynaptic actions mainly account for the tolerability profile of mirtazapine.

Of 5HT reuptake inhibition also occurs. That is, the SARI nefazodone may exploit the natural antagonism between 5HT1A and 5HT2A receptors by increasing 5HT through reuptake blockade while simultaneously blocking its actions at 5HT2A receptors. Normally, stimulation of 5HT2A receptors mitigates the stimulation of 5HT1A receptors (Figs. 7-16 and 7 — 17). This may also play out at the level of gene expression, where gene expression by 5HT1A stimulation alone (Fig. 7 — 18) is opposed by simultaneous stimulation of 5HT2A receptors (Fig. 7 — 19).

On the other hand, if 5HT2A receptors are blocked rather than stimulated, the normal inhibiting influence on 5HT1A receptor stimulation is lost. This may indirectly boost the effects of stimulating 5HT1A receptors, since it is no longer
FIGURE 7 — Shown here are icons for two of the serotonin 2A antagonist/reuptake inhibitors (SARIs). Nefazodone is the prototype agent in this class, which also includes trazodone. These agents also have a dual action, but the two mechanisms are different from the dual actions of the serotonin norepinephrine reuptake inhibitors (SNRIs). The SARIs act by potent blockade of serotonin 2A (5HT2A) receptors, combined with less potent serotonin reuptake inhibitor (SRI) actions. Nefazodone also has weak norepinephrine reuptake inhibition (NRI) as well as weak alpha 1 adrenergic blocking properties. Trazodone also contains antihistamine properties and alpha 1 antagonist properties but lacks the NRI properties of nefazodone.
FIGURE 7 — 15. This diagram shows the dual actions of the serotonin 2A antagonist/reuptake inhibitor (SARI) nefazodone. This agent acts both presynaptically and postsynaptically. Presynaptic actions are indicated by the serotonin reuptake inhibitor (SRI) portion of the icon, which is inserted into the serotonin reuptake pump, blocking it. Postsynaptic actions are indicated by the serotonin 2A receptor antagonist portion of the icon (5HT2A), inserted into the serotonin 2 receptor, blocking it. It is believed that both actions contribute to the antidepressant actions of nefazodone. Blocking serotonin actions at 5HT2A receptors may also diminish side effects mediated by stimulation of 5HT2A receptors when the SRI acts to increase 5HT at all receptor subtypes. The serotonin 2A antagonist properties are stronger than the serotonin reuptake properties, so serotonin antagonism predominates at the 5HT2A receptor.
mitigated by 5HT2A stimulation (Fig. 7-20). This same phenomenon may occur at the gene level as well (Fig. 7 — 21).

The SARI nefazodone may therefore not mediate its therapeutic actions merely by blocking 5HT2A receptors. In fact, selective 5HT2A antagonists have been tested in depression and have not been shown to be particularly efficacious antidepressants. The action of increasing 5HT via reuptake inhibition, leading to stimulation of 5HT1A receptors, may therefore be an important part of nefazodone's action. Without 5HT1A stimulation, 5HT2A antagonism would have nothing to potentiate. This principle will be discussed in further detail in the section on antidepressant combinations in which SSRIs are combined with other 5HT2A antagonists such as the atypical antipsychotics for resistant cases of depression. Combining indirect 5HT1A agonism with direct 5HT2A antagonism is another example of "intramolecular polypharmacy," exploiting the synergy that exists between these two mechanisms and again suggesting that two antidepressant mechanisms may sometimes be better than one.

When 5HT reuptake is inhibited selectively, as with the SSRIs, it causes essentially all serotonin receptors to be stimulated by the increased levels of 5HT that result. Although this has proved to be quite useful for treating depression and other disorders, it also has its costs. For example, we have discussed how stimulation of 5HT1A receptors in the raphe may help depression (Fig. 5 — 52), but how stimulating 5HT2A and 5HT2C receptors in the limbic cortex may cause agitation or anxiety (Figs. 5 — 53 and 5 — 54), and how stimulating 5HT2A receptors in the spinal cord may lead to sexual dysfunction (Fig. 5 — 57). Thus, an agent that combines 5HT
reuptake blockade with stronger 5HT2A antagonism would theoretically reduce the undesired actions of 5HT when it stimulates 5HT2A receptors. In this case, competition between 5HT reuptake blockade and stronger 5HT2A antagonism results in net antagonism at the 5HT2A receptor. In fact, the SARI nefazodone thus theoretically lacks the potential to cause sexual dysfunction, and usually also insomnia and anxiety, associated with the SSRIs.

Clinical experience suggests that nefazodone may also be useful in panic disorder, posttraumatic stress disorder, and generalized anxiety disorder, but without the 5HT2A-activating side effects associated with the SSRIs.

Trazodone is the original member of the SARI group of antidepressants. It also blocks alpha 1 receptors and histamine receptors (Fig. 7 — 14). Perhaps because of its histamine receptor blocking properties, it is extremely sedating. For this reason, its antidepressant use tends to be limited, yet it is well accepted as an excellent non-dependence-forming hypnotic, but it was never actually marketed for this indication. Its sedative hypnotic doses are generally lower than its effective antidepressant doses. Trazodone is used mostly as an adjunct to antidepressants because it not only increases the tolerability of SSRIs by blocking their side effects associated with stimulating 5HT2A receptors, such as insomnia and agitation, but it also can enhance the therapeutic efficacy of SSRIs, perhaps by exploiting the synergy of blocking 5HT2A receptors while stimulating 5HT1A receptors as discussed above. A rare but troublesome side effect of trazodone is priapism (prolonged erections in men, usually painful), which is treated by injecting alpha adrenergic agonists into the penis to reverse the priapism and prevent vascular damage to the penis.
FIGURE 7 — 18. Synergy between 5HT1A stimulation and 5HT2A antagonism—part 3. The molecular consequences of 5HT1A stimulation alone, shown here, result in a certain amount of gene expression corresponding to the pharmacological actions shown in Figure 7 — 16. Serotonin (5HT) occupancy of its 5HT1A receptor (top red circle) causes a certain amount of gene transcription (see bottom red circle on the right). The 5HT1A receptor is coupled to a stimulatory G protein (Gs) and adenylate cyclase (AC), which produces the second messenger cyclic AMP from ATP. This in turn activates protein kinase A (PKA), so that transcription factors such as cyclic AMP response element binding protein (CREB) can activate gene expression (mRNAs).

Nefazodone is in clinical testing as an extended-release formulation, which will reduce its administration to once daily and may also reduce its side effects. YM992 is another serotonin 2A antagonist with serotonin reuptake inhibition properties that is in testing as an antidepressant. Other more selective 5HT2 antagonists have been tested and discarded as potential antidepressants, including ritanserin and amesergide. However, MDL-100907 and SR46349 are selective 5HT2A antagonists in testing for schizophrenia. Furthermore, drugs with serotonin 2A antagonist properties but also dopamine antagonist properties, called serotonin-dopamine antagonists, or atypical antipsychotics, are in testing for bipolar disorder and for treatment-resistant depression. They will be discussed in further detail in the sections of this chapter below on bipolar disorder/antidepressant combinations. Agents with 5HT2A antagonist properties but also 5HT1A agonist properties are in testing as potential novel antidepressants; these include flibanserin, and possibly adatsanserin and BMS181,101.

New Antidepressants in Development

Currently, what is needed is an antidepressant that has onset of action faster than 2 to 8 weeks and has efficacy in more than two out of three patients. That efficacy
The molecular consequences of 5HT1A receptor stimulation concomitant with 5HT1A receptor stimulation is to reduce the gene expression of 5HT1A stimulation alone (i.e., that shown in Fig. 7—18). These molecular consequences correlate with the pharmacologic actions of simultaneous 5HT1A and 5HT2A stimulation shown in Figure 7—17. Simultaneous activation of the 5HT2A receptor by serotonin (on the right) will alter the consequences of activating 5HT1A receptors in a negative way and reduce the gene expression of 5HT1A receptors acting alone (Fig. 7—18). Thus, occupancy of the 5HT2A receptor (top circle) causes coupling of a stimulatory G protein (Gs) with the enzyme phospholipase C (PLC). This, in turn, activates calcium flux and converts phosphatidylinositol (PI) into diacylglycerol (DAG). This activates the enzyme phosphokinase C (PKC), which has an inhibitory action on phosphokinase A (PKA). This reduces the activation of transcription factors such as cyclic AMP response element binding protein (CREB) and leads to a decrease in gene expression (bottom red circle).

should be robust, causing remission, not response, and sustaining that remission for longer periods of time and in a larger proportion of patients than current antidepressants. Several theoretical candidates are in development, and some related to the mechanisms discussed above have already been mentioned. A sampling of other potential candidate antidepressants is given below. Most are variations on the theme of modulating either adrenergic neurons or serotonergic neurons with novel pharmacological mechanisms. Others attempt to achieve antidepressant actions by modulating peptide systems.

**Monoaminergic Modulators**

*Beta agonists.* Beta adrenergic receptors can be rapidly down regulated by agonists and if this is desired for an antidepressant action, beta agonists may be useful. To date, it has not been possible to identify beta 1 or beta 2 agonists that successfully penetrate the brain and yet are not cardiotoxic. Pursuing safer beta 1 and beta 2
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FIGURE 7-20. Synergy between 5HT1A stimulation and 5HT2A antagonism -part 5. If 5HT2A receptors are pharmacologically blocked rather than stimulated, they can no longer inhibit 5HT1A actions. Thus, 5HT1A receptors are chsinhibited (compare with Figs. 7-16 and 7-17).

agonists, perhaps as partial agonists, may optimize the pharmacological properties. However, beta 3 agonists such as SR58611 show preclinical efficacy as antidepressants and are in preliminary clinical testing.

Second messenger systems. Enhancing adrenergic functioning distal to the receptor occupancy site can theoretically be accomplished by targeting either the G proteins or the adenylate cyclase enzyme. Both types of agents are under development. Rolipram has shown promise in the past as an antidepressant that blocks the destruction of cyclic adenosine monophospate (cAMP) second messengers. Lithium mimetics that act on monoamine receptor G proteins or on enzymes regulating phosphatidyl inositol second messenger systems are being tested preclinically. It may turn out fortuitously that some of the anticonvulsants known or suspected to be useful for bipolar disorder, including depression, act on second messenger systems. Further exploitation of this approach may have to await clarification of the biochemical cascade that regulates critical gene expression in monoaminergic neurons and their targets.

5HT1A agonists, partial agonists and antagonists. Although many 5HT1A agonists have been extensively tested in clinical trials, none has made it to the market as an antidepressant, and only one has been approved as a generalized anxiolytic. Several 5HT1A agonists and partial agonists have been dropped from clinical development, but others still survive in clinical research. Gepirone ER, a chemical cousin of bus-
FIGURE 7 — 21. Synergy between 5HT1A stimulation and 5HT2A antagonism—part 6. The molecular consequences of 5HT1A receptor disinhibition by 5HT2A receptor blockade is shown here, namely enhanced gene expression. These molecular events are the consequence of the pharmacological actions shown in Figure 7 — 20. Simultaneous inhibition of the 5HT2A receptor on the right can stop the negative consequences that 5HT2A receptor stimulation by 5HT can have on gene expression, as shown in Figure 7 — 19. Thus, gene expression of the 5HT1A receptor (Fig. 7 — 18) is enhanced when 5HT2A receptors are blocked (bottom red circle) rather than diminished when they are stimulated (Fig. 7 — 19). The molecular basis of these effects is best reviewed by comparing Figures 7 — 18, 7 — 19, and 7 — 21. The pharmacological basis of these effects is best reviewed by comparing Figures 7 — 16, 7-17, and 7-20.

pirone, is continuing in clinical development in the United States and tandospirone in Japan. Ipsapirone, sunepitron, transdermal buspirone, and others have been dropped from clinical development, although there may be some continuing interest in flesinoxan or others.

Theoretically, a 5HT1A antagonist might be a rapid-onset antidepressant owing to immediate disinhibition of the serotonin neuron. This has been demonstrated preclinically, but no selective 5HT1A antagonist has undergone clinical testing in depression.

**Serotonin and dopamine reuptake inhibition.** Dual reuptake blockers of both serotonin and dopamine are in clinical testing. Although the SSRI sertraline has some dopamine reuptake inhibition as well as more potent serotonin reuptake inhibition, min-aprine and bazinaprine have more potent dopamine actions and are thus dual serotonin/dopamine agents.

**Serotonin 1D antagonists.** Theoretically, a 5HT1A antagonist should rapidly disinhibit the serotonin neuron and be a rapid-onset antidepressant. One such compound CP-448,187 is entering clinical development.
Neurokinin Antagonists

As explained in Chapter 5, theoretical considerations and some serendipitous clinical observations suggest that neurokinin antagonists, especially NK1 antagonists (i.e., substance P antagonists) may be novel antidepressants. Thus clinical testing is underway on NK1 antagonists including SR140333, MK-869, L-760,735, L-733,060, CP-96,345, and CP-122,721, as well as several others; NK2 antagonists such as SR48968 and GR-159,897; and NK3 antagonists such as SR142801.

Novel Neurotransmitter Mechanisms

Other potentially novel antidepressants in clinical testing target different neurotransmitter systems, including sigma receptors, peptides such as neurotensin or chole-cystokinin, and endogenous reward systems such as anandamide. These are in their very early testing phase.

Herbs

Herbal medicines such as hypericum, the active ingredient in St. John's wort, are used widely throughout the world, although never proven to be antidepressants by the same level of scrutiny as drugs marketed as antidepressants, such as TCAs and SSRIs. However, legitimate high-standard clinical testing is in progress to see whether herbs, especially St. John's wort, will prove to be antidepressants when held up to the same scrutiny that any drug undergoes prior to being marketed as an antidepressant. Recent reports that St. John's wort may have some toxic effect on reproductive functioning may mitigate the enthusiasm for this approach, however. One study suggests that it negatively affects fertility in both men and women. In addition, there is some evidence for mutation of the gene in sperm cells that may possibly increase risk to the developing fetus. Therefore, pregnancy is not currently recommended while taking these herbs.

Mood-Stabilizing Drugs

Lithium, the Classical Mood Stabilizer

Mood disorders characterized by elevations of mood above normal as well as depressions below normal are classically treated with lithium, an ion whose mechanism of action is not certain. Candidates for its mechanism of action are sites beyond the receptor in the second messenger system, perhaps either as an inhibitor of an enzyme, called inositol monophosphatase, involved in the phosphatidyl inositol system as a modulator of G proteins, or even as a regulator of gene expression by modulating protein kinase C (Fig. 7 — 22).

Lithium not only treats acute episodes of mania and hypomania but was the first psychotropic agent shown to prevent recurrent episodes of illness. Lithium may also be effective in treating and preventing episodes of depression in patients with bipolar disorder. It is least effective for rapid cycling or mixed episodes. Overall, lithium is effective in only 40 to 50% of patients. Furthermore, many patients are unable to tolerate it because of numerous side effects, including gastrointestinal symptoms.
The mechanism of action of lithium is not well understood but is hypothesized to involve modifying second messenger systems. One possibility is that lithium alters G proteins and their ability to transduce signals inside the cell once the neurotransmitter receptor is occupied by the neurotransmitter. Another theory is that lithium alters enzymes that interact with the second-messenger system, such as inositol monophosphatase, or others.

such as dyspepsia, nausea, vomiting, and diarrhea, as well as weight gain, hair loss, acne, tremor, sedation, decreased cognition, and incoordination. There are also long-term adverse effects on the thyroid and kidney. Lithium has a narrow therapeutic window, requiring monitoring of plasma drug levels.

Anticonvulsants as Mood Stabilizers

Based on theories that mania may "kindle" further episodes of mania, a logical parallel with seizure disorders was drawn, since seizures can kindle more seizures. Thus, trials of several anticonvulsants, beginning with carbamazepine, have been conducted, and several are showing indications of efficacy in treating the manic phase of bipolar disorder (Table 7 — 1). Only valproic acid, however, is actually approved for this indication.

The mechanism of action of anticonvulsants remains poorly characterized, both in terms of their anticonvulsant effects or their antimanic/mood stabilizing effects. They may even have multiple mechanisms of action. At the cell membrane, anticonvulsants appear to act on ion channels, including sodium, potassium, and calcium channels. By interfering with sodium movements through voltage-operated sodium
channels, for example, several anticonvulsants cause use-dependent blockade of sodium inflow. That is, when the sodium channels are being "used" during neuronal activity such as seizures, anticonvulsants can prolong their inactivation, thus providing anticonvulstant action. Whether such a mechanism is also the cause of the mood-stabilizing effects of anticonvulsants is yet unknown.

When ion channels are inactivated, this may result in changes of both excitatory and inhibitory neurotransmission. Glutamate is the universal excitatory neurotransmitter and gamma-aminobutyric acid (GABA) is the universal inhibitory neurotransmitter. In particular, anticonvulsants appear to modulate the effects of the inhibitory neurotransmitter GABA by augmenting its synthesis, augmenting its release, inhibiting its breakdown, reducing its reuptake into GABA neurons, or augmenting its effects at GABA receptors. Some of these actions may be the consequence of anticonvulstant actions at ion channels.

Anticonvulsants may also interfere with neurotransmission by the excitatory neurotransmitter glutamate, in particular by reducing its release. Simply put, inhibitory neurotransmission with GABA may be enhanced and excitatory neurotransmission with glutamate may be reduced by anticonvulsants.

Other actions of some anticonvulsants include inhibition of the enzyme carbonic anhydrase, negative modulation of calcium channel activity, and actions on second messenger systems, including inhibition of phosphokinase C. Beyond the second messenger, there is the possibility that second messenger systems may be affected, analogously to what is hypothesized for lithium.

Valproic acid. Although its exact mechanism of action remains uncertain, valproic acid (also valproate sodium, or valproate) may inhibit sodium and/or calcium channel function and perhaps thereby boost GABA inhibitory action as well as reduce glutamate excitatory action (Fig. 7 — 23). A unique and patented pharmaceutical formulation of valproic acid, called Depakote, reduces gastrointestinal side effects.

The Depakote form of valproic acid is approved for the acute phase of bipolar disorder. It is also commonly used on a long-term basis, although its prophylactic effects have not been as well established. Valproic acid is now frequently used as a first-line treatment for bipolar disorders, as well as in combination with lithium for patients refractory to lithium monotherapy and especially for patients with rapid cycling and mixed episodes. Oral loading can lead to rapid stabilization, and plasma levels must be monitored to keep drug levels within the therapeutic range.

Valproic acid can have unacceptable side effects, such as hair loss, weight gain, and sedation. Certain problems can limit valproic acid's usefulness in women of child-bearing potential, including the fact that it can cause neural tube defects in

Table 7 — 1. Anticonvulsants used to treat bipolar disorder

<table>
<thead>
<tr>
<th>Anticonvulsants used to treat bipolar disorder</th>
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<tbody>
<tr>
<td>valproic acid (Depakote)</td>
</tr>
<tr>
<td>carbamazepine</td>
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<tr>
<td>lamotrigine</td>
</tr>
<tr>
<td>gabapentin</td>
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<td>topiramate</td>
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FIGURE 7 — 23. Shown here is an icon of valproic acid’s pharmacologic actions. By interfering with calcium channels and sodium channels, valproate is thought both to enhance the inhibitory actions of gamma aminobutyric acid (GABA) and to reduce the excitatory actions of glutamate.

FIGURE 7 — 24. Shown here is an icon of carbamazepine’s pharmacologic actions. By interfering with sodium and potassium, carbamazepine is thought to enhance the inhibitory actions of gamma aminobutyric acid (GABA).

the developing fetus. Menstrual disturbances, polycystic ovaries, hyperandrogenism, obesity, and insulin resistance may also be associated with valproic acid therapy.

Carbamazepine. The anticonvulsant carbamazepine was actually the first to be shown to be effective in the manic phase of bipolar disorder, but it has not been approved for this use by regulatory authorities such as the U.S. Food and Drug Administration (FDA). Its mechanism of action may be to enhance GABA function, perhaps in part by actions on sodium and/or potassium channels (Fig. 7 — 24). Because its efficacy is less well documented and its side effects can include sedation and hematological abnormalities, it is not as well accepted for first-line use in the treatment of mood disorders as either lithium or valproic acid.

Lamotrigine. Lamotrigine is approved as an anticonvulsant but not as a mood stabilizer. It is postulated to inhibit sodium channels and to inhibit the release of glu-
FIGURE 7 — 25. Shown here is an icon of lamotrigine’s pharmacologic actions. By interfering with sodium channels, lamotrigine is thought to reduce the excitatory actions of glutamate.

FIGURE 7 — 26. Shown here is an icon of gabapentin’s pharmacologic actions. Gabapentin is thought to act by inhibiting the reuptake of gamma aminobutyric acid (GABA) into GABA terminals (shown as GRI for GABA reuptake inhibition). This enhances the inhibitory actions of GABA.

tamate (Fig. 7 — 25). Numerous reports suggest that lamotrigine is not only able to stabilize bipolar manic and mixed episodes but it may also be useful for the depressive episodes of this disorder. Further testing of lamotrigine’s safety and efficacy in mood disorders is ongoing.

Gabapentin. This compound was synthesized as a GABA analogue but turned out not to directly modulate the GABA receptor. It may well interact at the GABA transporter and increase GABA levels (Fig. 7 — 26). It also decreases glutamate levels. It is approved as an anticonvulsant and was originally observed to improve mood and quality of life in seizure disorder patients. Numerous studies suggest efficacy in the manic phase of bipolar disorder, and further clinical evaluation as a mood stabilizer is ongoing. A gabapentin analogue called pregabalin is also undergoing clinical evaluation as an anticonvulsant and as a mood stabilizer.

Topiramate. Topiramate is another compound approved as an anticonvulsant and in clinical testing as a mood stabilizer. Its mechanism of action appears to be to enhance
GABA function and reduce glutamate function by interfering with both sodium and calcium channels. In addition, it is a weak inhibitor of carbonic anhydrase (Fig. 7 — 27). Topiramate's mood-stabilizing actions may occur at lower doses than its anticonvulsant actions. This compound also has the interesting side effect of weight loss in some patients, a most unique effect among mood stabilizers, which generally cause weight gain.

Other Mood Stabilizing Drugs

Benzodiazepines. Benzodiazepines have anticonvulsant actions, especially intravenous diazepam and oral clonazepam. They are also sedating. Both of these actions have led to the use of benzodiazepines for the treatment of mood disorders, especially as adjunctive treatment for agitation and psychotic behavior during the phase of acute mania. Benzodiazepines are also broadly used in anxiety and sleep disorders.

Antipsychotics. Classical neuroleptics (such as haloperidol and the phenothiazine chlorpromazine) have long played a role in the treatment of agitation and the psychosis of mania. More recently, the atypical antipsychotics (such as risperidone, olanzapine and guetiapine) have begun to replace the older neuroleptics and assume an important adjunctive role in the treatment of bipolar disorders. Atypical antipsychotics may also improve mood in schizophrenia. Currently, the atypical antipsychotics are becoming more widely used for management of the manic phase of bipolar disorder Clinical studies are also ongoing to determine the role of these agents in the long-term management of bipolar disorder, including first-line use, maintenance treatment, and use in combination with mood stabilizers for treatment-resistant cases, especially mixed and rapid cycling cases.

Drug Combinations for Treatment-Resistant Patients - Rational Polypharmacy

So far, we have discussed many individual members of the "depression pharmacy" (Fig. 7 — 28). More than two dozen different agents acting by eight distinct mechanisms are thus useful for treating the typical case of depression (Fig. 7 — 29). However, psychopharmacologists are increasingly being called on to provide treatment for patients who do not respond to their initial treatment with one or another of the various antidepressants available from the depression pharmacy (Figs. 7 — 28 and 7 — 29). The following section is a somewhat complex discussion of how different drugs are combined to treat depression and bipolar disorders, and may not be of interest to the novice. Thus, some readers may wish to skip this section and jump ahead to the section on electroconvulsive therapy.

The most frequent strategy for managing patients who do not respond to several different antidepressant monotherapies is to augment treatment with a second agent. Such treatment-resistant (sometimes also called treatment-refractory) cases have classically been approached with an algorithm, first trying single agents from different pharmacological classes (Fig. 7 — 29) and then boosting single agents with a second drug, making for a variety of possible drug combinations (Figs. 7 — 30 through 7 — 57). The three augmenting agents that have been most studied are lithium, thyroid hormone, and buspirone. Other augmenting strategies discussed here are commonly
FIGURE 7 — 27. Shown here is an icon of topiramate's pharmacologic actions. By interfering with calcium channels and sodium channels, topiramate is thought both to enhance the inhibitory actions of gamma aminobutyric acid (GABA) and to reduce the excitatory actions of glutamate. Topiramate is also a carbonic anhydrase inhibitor (CAI) and as such has independent anticonvulsant actions.

employed in practice, but their use is often based more on art and anecdote than on scientific studies.

Lithium and Mood Stabilizers as Augmenting Agents

Lithium is the classical augmenting agent for unipolar depression resistant to first-line treatment with antidepressants (classic combo in Fig. 7 — 30). Lithium may boost the antidepressant actions of first-line antidepressants by acting synergistically on second messenger systems. Early studies indicate that the anticonvulsant class of mood stabilizers can also augment inadequate treatment responses to first-line antidepressants. Lithium and anticonvulsants are also used in combination with antidepressants for bipolar depression; however, in this disorder the mood stabilizers are the first-line treatment and antidepressants are given to augment inadequate response to a mood stabilizer rather than the other way around (see discussion of combination treatments for bipolar disorders below).

Thyroid Hormone as an Augmenting Agent

Since thyroid illness is commonly associated with depression, especially in women, it has long been observed that treating the thyroid abnormalities also can reverse the depression. This is especially true for treating hypothyroidism with thyroid hormone replacement (either T3 or T4). It has even been observed that giving supplemental thyroid hormone to depressed patients unresponsive to first-line antidepressants but without overt hypothyroidism can boost the antidepressant response of the first-line antidepressant (thyroid combo in Fig. 7 — 30). Thyroid hormone is also commonly administered to bipolar patients resistant to mood stabilizers, particularly those with rapid cycling (see discussion of combinations for bipolar disorders below).
FIGURE 7 — 28. There are many treatments for depression, indicated here as therapies on the shelf of the depression pharmacy. Many of these treatments are used as single interventions in the treatment of depression. The therapies include selective norepinephrine reuptake inhibitors (selective NRIs); serotonin 1A receptor agonists (5HT1A agents) interpersonal psychotherapy (IPT); serotonin antagonists/reuptake inhibitors (SARIs); thyroid hormone (TH) or estrogen; electroconvulsive therapy (ECT); dopaminergic agonists such as pramipexole and dopamine releasers/stimulants such as amphetamine and methylphenidate DA/stimulants; lithium (Li) or other mood stabilizers; serotonin selective reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs); norepinephrine and dopamine reuptake inhibitors (NDRIs); monoamine oxidase inhibitors (MAOIs); serotonin norepinephrine reuptake inhibitors (SNRIs); cognitive therapy (psychotherapy) and alpha 2 antagonists.

Buspirone, the Serotonin 1A Augmenting Agent

The serotonin 1A partial agonist buspirone, whose primary use is in generalized anxiety disorder, is also used as a popular augmenting agent for treatment-resistant depression, particularly in North America (serotonin 1A combo in Fig. 7 — 30). Its potential mechanism of action as an antidepressant augmenting agent is shown in Figures 7 — 31 to 7 — 33.

If serotonin is very low or depleted from serotonergic neurons in depression, there would not be much of it released for an SSRI to block its reuptake (Fig. 7 — 31). Thus, there would theoretically be inadequate desensitization of somatodendritic 5HT1A autoreceptors. Unlike the SSRIs, which are all dependent for their actions on the endogenous release of serotonin, buspirone is not dependent on serotonin levels because it has direct actions on 5HT1A receptors (Fig. 7 — 32). Thus, buspirone may be able to "kick start" the desensitization process directly. Initially,
Antidepressant monotherapies organized by mechanism of action. There are over two dozen agents acting by eight distinct pharmacological mechanisms. These include antidepressants that have single neurotransmitter action (the five SSRIs and the selective NRI reboxetine); agents that have dual actions on the same or similar neurotransmitter system (the SARI nefazodone and the NDRI bupropion); and agents that have dual actions (TCAs, MAOIs, the dual SNRI venlafaxine, and the alpha 2 antagonist mirtazapine).

Buspirone also slows neuronal impulses, which may also help the neuron to replete its serotonin (Fig. 7 — 32).

Thus, buspirone is synergistic with the SSRIs (Fig. 7 — 33). To the extent that buspirone is a partial agonist and thus partially blocks the 5HT1A autoreceptors, it...
Unipolar Combos

Single Neurotransmitter Monotherapy
- SSRI
- NDRI
- NRI
- SARI

Multiple Neurotransmitter Monotherapy
- SNRI
- Alpha 2 antagonist
- MAOI
- TCA

Classic Combo
- 1st line agent + Li (?valproate, mood stabilizers)

Thyroid Combo
- 1st line agent + T3/T4

Serotonin 1A Combo
- 1st line agent + buspirone (?pindolol)

Cautious Combo
- TCA + MAOI

E2 estrogen combo
- 1st line agent + estrogen

Insomnia anxiety combo
- 1st line agent + zaleplon / zolpidem / benzodiazepine
FIGURE 7-31. *Mechanism of action of buspirone augmentation -part 1.* SSRIs act indirectly by increasing synaptic levels of 5HT that has been released there. If 5HT is depleted, there is no 5HT release, and SSRIs are ineffective. This has been postulated to be the explanation for the lack of SSRI therapeutic actions or loss of therapeutic action of SSRI ("poop out") in some patients.
FIGURE 7 — 32. Mechanism of action of buspirone augmentation—part 2. Shown here is how buspirone may augment SSRI action both by repleting 5HT and by directly desensitizing 5HT1A receptors. One theoretical mechanism of how 5HT is allowed to reaccumulate in the 5HT-depleted neuron is the shutdown of neuronal impulse flow. If 5HT release is essentially turned off for a while so that the neuron retains all the 5HT it synthesizes, this may allow repletion of 5HT stores. A 5HT1A partial agonist such as buspirone acts directly on somatodendritic autoreceptors to inhibit neuronal impulse flow, possibly allowing repletion of 5HT stores. Also, buspirone could boost actions directly at 5HT1A receptors to help the small amount of 5HT available in this scenario accomplish the targeted desensitization of 5HT1A somatodendritic autoreceptors that is necessary for antidepressant actions.
FIGURE 7 — 33. Mechanism of action of buspirone augmentation—part 3. Shown here is how buspirone potentiates ineffective SSRI action at 5HT1A somatodendritic autoreceptors, resulting in the desired disinhibition of the 5HT neuron. This combination of 5HT1A agonists plus SSRIs may be more effective, not only in depression but also in other disorders treated by SSRIs, such as obsessive-compulsive disorder and panic.

may act even faster than an SSRI. Blockade of these receptors immediately disinhibits them, whereas stimulation of them causes delayed disinhibition due to the time it takes for them to desensitize.

Pindolol, Another Serotonin 1A Augmenting Agent

The idea of blocking 5HT1A somatodendritic autoreceptors is also exploited by pindolol, a well-known beta adrenergic blocker that also is an antagonist and very partial agonist at 5HT1A receptors. Preclinical studies suggest that pindolol can immediately disinhibit serotonin neurons, leading to the proposal that it may be a rapid onset antidepressant or augmenting agent. Some clinical studies do suggest that pindolol augmentation may speed the onset of action of SSRIs or may boost
inadequate response to SSRIs, but not all investigators agree. Nevertheless, 5HT1A antagonists are in development as potential novel and rapid-acting antidepressants.

**Monoamine Oxidase inhibitor/Tricyclic Antidepressant Combinations**

One old-fashioned augmentation strategy that has fallen out of favor in recent years is to combine with great caution a TCA and an MAO inhibitor (the cautious combo in Fig. 7 — 30). Given its potential dangers (e.g., sudden hypertensive episodes, orthostatic hypotension, drug and dietary interactions, obesity), as well as the wide variety of other antidepressant combinations available today, this combination is rarely necessary or justified.

**Estrogen and Reproductive Hormones as Antidepressant Augmenting Agents**

Another hormone combination therapy is to combine a first-line antidepressant, especially an SSRI, with estrogen replacement therapy in perimenopausal or postmenopausal women refractory to treatment with antidepressant monotherapies (the estrogen combo in Fig. 7 — 30). Unfortunately, there are few if any controlled clinical trials to provide guidance on how to combine estrogen with antidepressants. Numerous case reports and anecdotes from clinicians demonstrate that some women respond to estrogen who do not respond to antidepressants, and other women respond to estrogen plus an antidepressant who do not respond to antidepressants alone. Since estrogen is itself a direct activator of transcription, it may be able to synergize at the genomic level with the transcription activated by SSRIs (Fig. 7 — 34) to produce a molecular result greater than that which the SSRIs can produce alone.

Other uses of the reproductive hormone approach are to avoid cyclical use of estrogen/progestins, eliminate progestins, add testosterone, or add dihydroepiandrosterone (DHEA). Such approaches remain anecdotal and require controlled studies of how they may be useful augmenting agents for antidepressants both in women and in men.

**Insomnia/Anxiety Combinations**

Insomnia is a common comorbid condition with depression, and frequently is made worse by antidepressants, particularly the SSRIs. When insomnia persists despite adequate evaluation and attempts to reduce it by other approaches, it is often necessary to use a concomitant sedative-hypnotic, especially a short-acting nonbenzodiazepine with rapid onset such as zaleplon or zolpidem. At times a benzodiazepine sedative hypnotic such as triazolam or temazepam may be necessary. If anxiety persists during the day and cannot be otherwise managed, it may be necessary to add an anxiolytic benzodiazepine such as alprazolam or clonazepam. Use of sedative-hypnotics and anxiolytics should be short-term whenever possible.
FIGURE 7 — 34. Estrogen acts at receptors in the neuronal cell nucleus to directly **boost the transcription of genes.** This may be synergistic with the antidepressant actions of first-line antidepressant agents in activating transcription factors (TF) in some women.

**Bipolar Combinations**

Combination treatment with two or more psychotropic medications is the rule rather than the exception for bipolar disorders (bipolar combos in Fig. 7 — 35). First-line treatment is with either lithium or valproic acid. When patients fail to stabilize in the acute manic phase on one of these first-line treatments, the preferred second-
<table>
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<th>Bipolar Combos</th>
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<tr>
<td><strong>First Line Monotherapy</strong></td>
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<tr>
<td><strong>Second Line Monotherapy</strong></td>
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<tr>
<td><strong>Third Line Monotherapy</strong></td>
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<tr>
<td><strong>Atypical Combo</strong></td>
</tr>
<tr>
<td><strong>Benzod 'Assault Weapon' Combo</strong></td>
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<tr>
<td><strong>Neuroleptic 'Nuclear Weapon' Combo</strong></td>
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<td><strong>Mood Stabilizer Combo</strong></td>
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<td><strong>Antidepressant Combo</strong></td>
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line agent is an atypical antipsychotic. Atypical antipsychotics are even becoming first-line treatments for the manic phase of bipolar disorder.

If lithium, valproic acid, or atypical antipsychotic monotherapies are not effective in the acute situation, they can be used together (atypical combo in Fig. 7 — 35). If this is not effective, a benzodiazepine or a conventional antipsychotic (i.e., a neuroleptic) can be added to first- or second-line monotherapies, especially for the most disturbed patients (Fig. 7 — 35). That is, sedating benzodiazepines can be used for lesser degrees of agitation (benzo assault weapon in Fig. 7 — 35), but neuroleptic antipsychotics may be necessary for the most disturbed and out-of-control patients (nuclear weapon in Fig. 7-35). Neuroleptic antipsychotics should be restricted to the acute phase, and administered sparingly.

For maintenance treatment, failure of first-line mood stabilizers or second-line atypical antipsychotics to control symptoms adequately may lead to monotherapy trials with other anticonvulsants such as carbamazepine, lamotrigine, gabapentin, and topiramate (third-line monotherapy).

Therapeutic recommendations for maintenance treatment of bipolar disorder are undergoing rapid changes. In the recent past, lithium was the hallmark of this treatment, often with antidepressant co-therapy for patients prone to depression as well as mania and not adequately controlled by lithium alone. Now, however, several new therapeutic principles are guiding the treatment of bipolar disorders in the maintenance phase.

First, anticonvulsants, particularly valproic acid, are now considered excellent first-line choices along with lithium, although lithium is the only agent approved for such use.

Second, atypical antipsychotics are clearly second-line choices for maintenance therapy of bipolar disorder when one or more mood stabilizers alone or in combination are not adequate. Furthermore, atypical antipsychotics are also becoming first-line choices for bipolar maintenance as the safety and efficacy data from controlled trials continue to evolve.

Third, antidepressant treatments are not benign in this condition. Although many bipolar patients have been classically maintained on both lithium and an antidepressant, it is now recognized that antidepressants frequently decompensate bipolar patients, causing not only overt mania or hypomania, but also the problems of mixed mania and rapid cycling, which are much more difficult to recognize and treat. The trend today is to use antidepressants sparingly and if necessary, only in the presence of robust mood stabilization with mood stabilizers, atypical antipsychotics, or both. In fact, both mood stabilizers and atypical antipsychotics may prove to be useful for the depressed phase of bipolar illness, reducing or perhaps eliminating the need for potentially destabilizing antidepressants in bipolar patients. Thus, antidepressants are now relegated to third-line use in bipolar disorder, behind lithium or anticon-vulsant mood stabilizers and atypical antipsychotics. This is an antidepressant-sparing strategy for the treatment of bipolar disorder.

Combination treatments for maintenance of bipolar disorder can include two or more mood stabilizers; a mood stabilizer and an atypical antipsychotic; a mood stabilizer and/or atypical antipsychotic with a benzodiazepine; a mood stabilizer with thyroid hormone; and even a mood stabilizer and/or atypical antipsychotic with an antidepressant (Fig. 7 — 35).
A Rational Approach to Antidepressant Combinations with Other Antidepressants

In the current managed care era, the modern psychopharmacologist/psychiatrist may deal almost exclusively with patients resistant to conventional treatment approaches, since easier cases are handled by lower cost or primary care providers, and these difficult cases are selectively referred. Treating patients resistant to well documented strategies by using less well documented but pharmacologically and molecularly rational strategies is not for the novice, nor for those who wish to work within treatment guidelines for drugs with government regulatory approvals and with the documentation of numerous published controlled clinical trials. First-line monotherapies and combination therapies are summarized in Figure 7—36.

The rationale for proceeding to the use of combinations of two antidepressants is based on a number of factors. First, certain combinations of antidepressants can exploit theoretical pharmacologic and molecular synergies to boost monoaminergic neurotransmission. Second, some combinations of antidepressants have anecdotal and empirical evidence of safety and efficacy from uncontrolled use in clinical practice. Finally, the idea of using multiple pharmacologic mechanisms simultaneously for the most difficult cases is already a recognized therapeutic approach in other areas of medicine, such as the treatment of resistant bacterial and human immunodeficiency virus infections, cancer, and resistant hypertension. Later in this chapter we will describe three specific approaches to the management of patients resistant to first-line monotherapies and typical augmentation strategies, namely, the seroto-nergic strategy, the adrenergic strategy, and the dual-mechanism or "heroic" strategy.

Diagnosing treatment resistance. Many patients have a difficult time with antidepressants, and following a trial with several of drugs, it is easy to conclude that they are treatment-resistant. Prior to concluding that a patient is not responding to antidepressants and therefore truly treatment-resistant, however, it is necessary to carefully review the treatment history to rule out medication intolerance masquerading as medication resistance (e.g., many medications tried, but few adequate trials of full doses for 4 to 8 weeks). The solution to medication intolerance may be to augment with an antidepressant that cancels the side effects of the antidepressant that is not tolerable.

The other situation to rule out when establishing treatment resistance in depression is misdiagnosis as resistant unipolar depression when the patient is actually bipolar. That is, an apparently unipolar patient with drug-induced agitation may actually be a bipolar patient with antidepressant-induced rapid cycling or mixed mania of an unrecognized bipolar disorder. This situation will commonly be exacerbated by combining two antidepressants. The solution to this problem may, in fact, be to discontinue antidepressants and optimize treatment with mood stabilizers and atypical antipsychotics before using any antidepressant agent.

Principles of antidepressant combinations. The first principle of combination treatment with antidepressants is to combine mechanisms, not just drugs. That is, the important thing is the pharmacological mechanisms being combined; drugs are just the "mules" that carry mechanisms on their backs. Some drugs have one principal mech-
FIGURE 7 — 36. This figure summarizes both first-line monotherapies and the most commonly used combination therapies for unipolar depression. Note that antidepressant combinations at the far right and the end of the line are to be used after other strategies fail.

anism, others multiple mechanisms. Thus, combining two drugs may in fact be combining three or more mechanisms. Furthermore, there are many different drug mules that carry the same mechanisms, allowing for multiple approaches to achieving any given mixture of mechanisms by using several different combinations of drugs.

A second principle of antidepressant combination is to promote bad mathematics. That is, successful mixture of drug mechanisms leads to pharmacological synergy for antidepressant therapeutic actions (where $1 + 1 = 10$). Furthermore, knowing the mechanism of antidepressant side effects can lead to other successful mixtures of drug mechanisms where opposing side effect profiles promote tolerability (in other words, where $1 + 1 = 0$). The cleverest mixtures of antidepressants can yield both forms of bad mathematics at the same time, namely synergistic boost to efficacy along with improved tolerability achieved by canceling mutual side effects.

The third principle of antidepressant combinations is to exploit theoretically important synergies within the serotonin, norepinephrine, and even dopamine monoaminergic systems. Specifically, two independent pharmacologic actions at any one of the monoaminergic systems can be synergistic. Examples of this are combination of either serotonin or norepinephrine reuptake blockade with alpha 2 blockade, or 5HT reuptake blockade with serotonin 2A antagonism, as discussed earlier in this chapter. Specific examples of how to implement this approach for serotonin are given in Figure 7 — 37. Specific examples of how to implement this approach for norepinephrine and dopamine are given in Figures 7 — 38 to 7—43.
FIGURE 7-37. Synergy between serotonin reuptake inhibitors and serotonin 2A antagonists is commonly observed. Various specific drug combinations to implement this strategy in unipolar depression are shown here.

The other theoretically important synergy to exploit for treating resistant depression is that between serotonin and norepinephrine (e.g., Figs. 7—39 and 7—44). Thus, boosting neurotransmission at both monoamine systems with either a single drug or combinations of drugs can also boost therapeutic efficacy in treatment-resistant depression. Several specific examples of how to implement this strategy are given in Figures 7—45 to 7—57.

Synergy within the serotonergic system. Boosting serotonin neurotransmission has proved to be useful not only in treatment-resistant depression, but for treatment resistance within the whole family of "serotonin spectrum disorders," such as obsessive-compulsive disorder, panic disorder, social phobia, posttraumatic stress disorder, and bulimia.

A major example of pharmacologic synergy within the serotonin system is the 5HT2A antagonist strategy. This is shown in Figures 7 — 20 and 7 — 21 and was discussed earlier in the section on nefazodone and the SARIs. For this strategy, robust inhibition of serotonin reuptake by agents in the left column of Figure 7 — 37 is
Shown here are various drug combinations for use in treatment resistant unipolar depression to boost adrenergic neurotransmission, which include either norepinephrine, dopamine, or both.

Combined with robust inhibition of serotonin 2A receptors in the right column of Figure 7-37. These are not necessarily the only mechanisms combined by the specific agents shown, but this strategy is the common denominator across all pairings.

Perhaps the most commonly used example of the serotonin 2A strategy is the combination of an SSRI with trazodone. Clinicians have long recognized that trazodone will improve the agitation and insomnia often associated with SSRIs, allow high doses of the SSRI to be given, and consequently boost the efficacy of the SSRI not only in depression, but also in obsessive-compulsive disorder and other anxiety disorders. Thus, both types of bad math are in play here.

Perhaps the best documented example showing the enhanced efficacy of this serotonin 2A antagonist strategy is the use of the atypical antipsychotics to boost efficacy in nonpsychotic depression refractory to treatment with an SSRI.

Norepinephrine and synergy. Boosting noradrenergic neurotransmission may be useful not only in depression in general, but in partial responders as well, especially those with fatigue, apathy, and cognitive slowing. Several examples of how to boost noradrenergic neurotransmission beyond that of single agents alone are given in Figure 7 — 38. Thus, selective noradrenergic reuptake inhibitors such as reboxetine or non-selective noradrenergic reuptake inhibitors such as desipramine can be combined with the noradrenergic/dopaminergic agent bupropion. Also, bupropion or a noradrenergic reuptake inhibitor can be combined with a dopamine-releasing stimulant (such as amphetamine, methylphenidate, diethylpropion or phentermine) or with a
FIGURE 7—39. **Key to combos.** The figures from here to the end of the chapter will employ the visual key shown here. The depressed, unmedicated state is shown by faded colors representing neurotransmitter depletion. If any of the three monoamine neurotransmitters (SHT, NE, or DA) is boosted by one of the drugs in the combination being illustrated, its corresponding color will light up moderately. Thus, single boosting of SHT will moderately light up yellow; single boosting of NE will moderately light up purple; and single boosting of DA will moderately light up blue. Some of the combos have synergistic actions on the same monoamine neurotransmitter system. In such cases, the colors will be doubly lit up to represent the potential synergy of this approach by the brightest coloring of SHT (yellow), NE (purple), or DA (blue).

FIGURE 7—40. **Adrenergic combo 1: Bupropion** plus norepinephrine reuptake inhibitor (NRI). Here the NE actions of bupropion are double-boosted by the NRI (either selective reboxetine or nonselective desipramine, maprotilene, nortriptyline, or protriptyline). Dopamine is single-boosted by bupropion only.
FIGURE 7-41. **Adrenergic combo 2: Bupropion** can be combined with a **stimulant** such as *d*-amphetamine or methylphenidate. The stimulant will add a double dopamine boost to bupropion, which boosts dopamine in its own right. A single boost of norepinephrine from bupropion also is present.

FIGURE 7—42. **Adrenergic combo 3:** The actions of bupropion at dopamine neurons can be double-boosted by a direct-acting dopamine **D2 and D3 agonist** such as pramipexole. Norepinephrine is also single-boosted by bupropion.

FIGURE 7—43. **Adrenergic combo 4: NRI plus *d,l*-amphetamine.** In this case, the NRI action at NE is double-boosted by a mixture of amphetamine salts containing the *l* as well as the *d* form of amphetamine. The *l*-amphetamine causes NE release. In addition, DA will be single-boosted by the *d*-amphetamine, which causes DA release.

direct dopamine agonist such as pramipexole. Anecdotally, this may be especially useful for patients with retarded or melancholic depression or those who require an antidepressant concomitantly with a mood stabilizer for bipolar depression.

*The heroic strategy: boosting both serotonin and norepinephrine.* In the most refractory of all patients, it may be necessary to use both serotonin and adrenergic combination
FIGURE 7—44. A baker’s dozen of **heroic combos** of two antidepressants for treatment-resistant unipolar depression are shown here. Each individual-combination is explained in the figures that follow (Figs. 7-45 through 7-57).
FIGURE 7—45. Heroic combo 1, or "California rocket fuel": High-dose venlafaxine plus mirtazapine. This is a combination of antidepressants that has a great degree of theoretical synergy: reuptake blockade plus alpha 2 blockade; serotonin reuptake plus 5HT2A antagonism; 5HT actions plus NE actions. Specifically, 5HT is triple-boosted, with reuptake blockade, alpha 2 antagonism, and 5HT2A antagonism; NE is double-boosted, with reuptake blockade plus alpha 2 antagonism; and there may even be a bit of single boost to DA from reuptake blockade.

FIGURE 7-46. Heroic combo 2: High-dose venlafaxine plus NDRI (bupropion). Here, 5HT is single-boosted, NE is double-boosted, and DA is double-boosted.

FIGURE 7-47. Heroic combo 3: High-dose venlafaxine plus NRI. Here, 5HT is single-boosted, NE is double-boosted, and DA may be single-boosted. The NRI could be either selective reboxetine or a nonselective TCA such as desipramine, maprotiline, nortriptyline, or protriptyline.

strategies (heroic combo; Fig. 7—44). A baker's dozen of heroic combos are given in Figure 7—44 and shown graphically in Figures 7—45 through 7 — 57. These specific drug combinations all do the same thing to one extent or another, namely, boost or double-boost serotonin, norepinephrine, and/or dopamine. The net effects of these combinations are shown in different shades of color in Figures 7—45 through 7 — 57, with light colors representing no boost to the corresponding monoamine's neuro-
FIGURE 7-48. Heroic combo 4: **High-dose venlafaxine plus stimulant.** Here, 5HT and NE are single-boosted and DA is double-boosted. The stimulants could include d-amphetamine, methylphenidate, phentermine, or diethylpropion. It could also include direct-acting dopamine agonists such as pramipexole.

FIGURE 7—49. Heroic combo 5: **Venlafaxine plus nefazodone.** Serotonin will be double-boosted to a certain extent by nefazodone alone. At any dose of venlafaxine, the boosting of serotonin will be considerably enhanced. This enhancement of nefazodone's serotonin action can also be replicated by SSRIs, but citalopram may be the best tolerated. At high doses of venlafaxine, there will be not only boosting of 5HT but also single-boosting of NE and maybe DA.

FIGURE 7 — 50. Heroic combo 6: **Mirtazapine plus SSRI.** Here serotonin is double-disinhibited both by reuptake blockage and by alpha 2 antagonism; NE is also single-boosted.

transmission, medium-intensity colors representing a single boost to that monoamine's neurotransmission, and high-intensity colors representing a double boost (see figure key in Fig. 7 — 39). One of the most theoretically powerful combinations is that of high-dose venlafaxine with mirtazapine ("California rocket fuel" in Fig. 7—45; also Fig. 7—44). These drugs combine synergies on synergy, that is, reuptake
blockade plus alpha 2 blockade for double disinhibition, actions at 5HT and NE actions boosting 5HT at 5HT1A receptors yet blocking 5HT2A receptors.

The point is to use safe and rational drug combinations that exploit expected pharmacological and molecular synergies while even promoting mutual tolerabilities. Each of the combinations in Figure 7—44 is used clinically and has helped some patients but not others. Unfortunately, little scientific documentation of this empirical usefulness of such rational combinations is yet available, but many studies
FIGURE 7-54. Heroic combo 10: SSRI plus NRI. Here, 5HT and NE are both single-boosted. The preferred NRI is selective reboxetine, as there are no drug interactions. Nonselective TCAs that are preferential NRIs such as desipramine, maprotiline, nortriptyline, or protriptyline can be combined if plasma drug levels of the TCA are monitored, especially if fluoxetine or paroxetine is the SSRI chosen.

FIGURE 7-55. Heroic combo 11: SSRI plus NDRI (bupropion). Here 5HT, NE, and DA are all single-boosted.

FIGURE 7-56. Heroic combo 12: SSRI plus stimulant. Here, 5HT and DA are single-boosted. The stimulants could include \(d\)-amphetamine, methylphenidate, phentermine, or diethylpropion. The combo could also include direct-acting dopamine agonists such as pramipexole.

are ongoing and should clarify the best options for the most difficult cases in which the benefits of this approach outweigh the risks.

**Electroconvulsive Therapy**

Failure to respond to a variety of antidepressants, singly or in combination, is the key factor indicating consideration of electroconvulsive therapy (ECT). This is the only therapeutic agent for the treatment of depression that is rapid in onset and can
start after even a single treatment, typically within a few days. The mechanism is unknown but is thought to be related to the probable mobilization of neurotransmitters caused by the seizure. In experimental animals, ECT down-regulates beta receptors (analogous to antidepressants) but up-regulates 5HT2 receptors (opposite of antidepressants). Memory loss and social stigma are the primary problems associated with ECT and limit its use. There can also be striking regional differences across the various countries in the world in the frequency of ECT use and in ECT techniques. For example, ECT may be more commonly used in Europe and the United Kingdom and on the U.S. East Coast and less commonly used on the U.S. West Coast.

Electroconvulsive therapy is especially useful when rapid onset of clinical effect is desired and when patients are refractory to a number of antidepressant drugs. It is also very helpful in psychotic and bipolar depression and in postpartum psychosis. If the mechanism of the therapeutic action of ECT could be unraveled, it might lead to a new antidepressant drug capable of rapid onset of antidepressant effects or with special value for refractory patients. Until then, ECT will remain a valuable member of the therapeutic armamentarium for depression.

**Psychotherapy**

In recent years, modern psychotherapy research has begun to standardize and test selected psychotherapies in a manner analogous to the testing of antidepressant drugs in clinical trials. Thus, psychotherapies are now being tested by being administered according to standard protocols by therapists receiving standardized training and using standardized manuals, and also in standard "doses" for fixed duration. Such uses of psychotherapies are being compared in clinical trials with placebo or antidepressants. The results have shown that interpersonal psychotherapy and cognitive psychotherapy for depression may be as effective as antidepressants themselves in certain patients. Proof of the efficacy of certain psychotherapies is thus beginning to evolve.

Research is only beginning on how to combine psychotherapy with drugs. Although some of the earliest studies did not indicate any additive benefit of tricyclic antidepressants and interpersonal psychotherapy, recent studies are now demonstrat-
ing that there can be an additive benefit between psychotherapy and antidepressants. One recent study of nefazodone suggests that it is particularly effective when combined with cognitive behavioral psychotherapy for patients with chronic depression. Another study of nortriptyline suggests an additive benefit of interpersonal psychotherapy, particularly when looking at long-term outcomes. It is not known whether the addition of psychotherapy to antidepressant responders who are not in full remission might lead to remission and recovery, but this is an interesting possibility. Although psychotherapy is frequently employed on an empirical basis, it is not yet proven that its addition to the psychopharmacological treatment of patients resistant to antidepressant monotherapy treatment (either no response, or a response but not a remission) improves outcomes. As managed care reduces the availability of psychotherapy, mental health professionals are becoming increasingly dependent on a psychopharmacological approach. The rapidly evolving scientific demonstration of the benefit of adjunctive psychotherapy should provide much needed and welcome justification by showing who benefits from what kinds of psychotherapy combined with which specific antidepressants. Cognitive and behavioral psychotherapies are also of value as adjuncts to antidepressants for the treatment of anxiety disorders.

Summary

In this chapter, we have discussed the mechanisms of action of several of the newer classes of antidepressant drugs and mood stabilizers. The acute pharmacological actions of these agents on neurotransmitter receptors have been described. The reader should now understand the proposed mechanisms of action of dual reuptake inhibitors, alpha 2 antagonists, and serotonin 2A antagonists/serotonin reuptake inhibitors, as well as those of lithium and the anticonvulsant mood stabilizers for the treatment of bipolar disorder, particularly the acute manic phase.

We have reviewed antidepressant augmentation strategies, including the principles and several specific examples. Finally, we have touched on the use of electro-convulsive therapy and psychotherapy for the treatment of depression.

Although the specific pragmatic guidelines for use of these various therapeutic modalities for depression have not been emphasized, the reader should now have a basis for the rational use of antidepressant and mood-stabilizing drugs founded on application of principles of drug action on neurotransmission via actions at key receptors and enzymes.